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Protocol for a Randomized Sham-Controlled Double-blind Multicenter Efficacy Study of the Gelstix™ Nucleus Augmentation Device to treat Chronic Discogenic Low Back Pain

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Randomized Sham-Controlled Double-blind Multicenter Efficacy Study of the Gelstix™ Nucleus Augmentation Device to treat Chronic Discogenic Low Back Pain

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ABSTRACT

Introduction

Discogenic pain is the cause of pain in up to 40% of patients consulting a physician for low back pain. Consensus about treatment of chronic discogenic low back pain is lacking and the majority of treatment alternatives is supported by limited evidence, and fusion surgery is not proven to be superior to conservative treatment. We hypothesize that treatment with GelStix™ will lead to greater reduction in pain intensity at six months post-treatment compared to patients receiving sham treatment.

Methods and analysis

This is a parallel group, randomized sham-controlled double-blind, multicentre trial to assess whether the GelStix^{tm} device is superior to sham in reducing pain intensity in patients with chronic discogenic low back pain. The primary outcome will be the change in pain intensity between preoperative baseline and at six months post-intervention. Secondary outcomes include disability, quality of life, the patient's global impression of change scale, the use of pain medication, and the disc degeneration process assessed by means of MRI. For change in pain intensity, disability, health related quality of life, and disc height, mean values will be compared between groups using linear regression analysis, adjusted for treatment centre.

Ethics and dissemination

Ethics approval was obtained from the Ethics Committee of the Canton Ticino, Switzerland (CE2982) and by the Medical Ethical Committee Arnhem-Nijmegen, the Netherlands (2016-2944). Results will be disseminated through international publications in peer reviewed journals, in addition to international conference presentations.

Trial registration number NCT02763956

Protocol version 7.1, 18/11/2020

Keywords Back pain, pain management, musculoskeletal disorders

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ARTICLE SUMMARY

Strengths and limitations of this study

- ►This will be the first prospective, randomized, controlled, multicentre trial assessing effectivity and safety of the GelStix™ Nucleus Augmentation Device compared to a sham control in patients with lumbar discogenic pain that had no benefit from conservative care.
- ►Means to reduce risk of bias are implemented, which includes an a-priori sample size calculation, an explicitly stated primary hypothesis to be tested, methodological rigor, double-blinding, randomization, adequate concealment of group allocation and the assessment of the success of blinding in participants and observers.
- ►This is also the first study that assesses the disc degeneration process and disc height by means of Magnetic Resonance Imaging (MRI) one year after GelStix™ implantation versus sham.
- ►All participants will also be treated according to a protocolized physiotherapy.
- ►The limitations are those inherent to a prospective, randomized sham-controlled double-blind study, including strict exclusion criteria and thus limited generalizability (e.g., protrusions in contact with any nerve root at the symptomatic level or >5mm, an insufficient number of patients, and adherence to a strict protocol that does not necessarily reflect real word daily practice.

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INTRODUCTION

Background and rationale

Discogenic low back pain is characterized by persistent, predominantly centralized axial low back pain that worsens with axial loading. It is associated with intervertebral disc degeneration without herniation,[1–4] and is thought to be the cause of pain in up to 40% of patients consulting a physician for low back pain.[5–8] The water-binding capabilities of the intervertebral disc diminish with aging[9] leading to progressive shrinking of the nucleus pulposus and loss of elasticity.[9–12] The cartilaginous endplate vascular flow decreases due to a progressive loss in vascularization leading to accumulation of cellular waste products, and an increasingly acidic environment.[9,13] A low pH around the discus is associated with discogenic pain.[14,15]

Medical history, physical examination, and imaging (e.g. magnetic resonance imaging (MRI)) provide inadequate sensitivity and specificity to accurately diagnose discogenic pain.[16,17] Despite an ongoing debate, moderate evidence supports diagnostic accuracy of provocative discography.[18–20] While previous studies suggest that high-pressure provocative discography may accelerate disc degeneration,[21–23] a recently published study suggests that low-pressure provocative discography, performed according to International Association for the Study of Pain (IASP) criteria, does not accelerate disc degeneration.[24]

Consensus about treatment of chronic discogenic low back pain is lacking and the majority of treatment alternatives is supported by limited evidence.[1,4] Conservative management includes anti-inflammatory drugs, physiotherapy, and multidisciplinary biopsychosocial rehabilitation.[25] If conservative treatment fails, (minimally) invasive treatments are considered. Most minimally invasive treatments, such as intradiscal injections (e.g. with methylene blue) and thermal intradiscal/annular techniques (intradiscal electrothermal therapy (IDET), have been abandoned because of poor evidence.[26–28] A recent systematic review concluded that most minimal invasive treatments for discogenic low back have very low evidence; only biacuplasty has moderate evidence for a subgroup of patients with discogenic low back pain.[29]

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Fusion surgery and total disc replacement, although contemplated as possible therapies in some cases, are invasive interventions associated with risk of adjacent segment disorder and morbidity.[4,30] In addition, fusion surgery is not superior to conservative treatment with multidisciplinary biopsychosocial rehabilitation and physiotherapy.[31,32] Recently, with the emergence of new frequencies (burst, dorsal root ganglion stimulation, high frequency-10Hz), low back pain has become a good treatment option for neuromodulation. Considering the fact that neuromodulation is a more invasive treatment the need is great to find evidence for minimal invasive treatment for chronic discogenic low back pain.[33,34]

Therefore, treatment options filling the gap between conservative care and invasive surgical intervention are urgently needed. Currently the first studies are published showing effect of the use of platelet-rich plasma (PRP) and mesenchymal signaling cells (MSCs) for discogenic pain. Notably, no intervention has multiple RCT's published yet.[35] The implantation of hydrogels into the nucleus pulposus represents a promising regenerative intradiscal therapy, in particular in patients with early or moderate disc degeneration not responding to conservative care.[36,37] The hydrogel containing 'GelStix™ Nucleus Augmentation Device' (hereafter called GelStix™) is composed primarily of hydrolyzed polyacrylonitrile (HPAN). The GelStix™ is shaped in the form of an elongated matchstick and can be inserted percutaneously into the nucleus through a needle. Once implanted, the GelStix™ absorbs the body's own fluids and expands around tenfold in volume (see Fig. 1).

Insert here Figure 1

The GelStix™ material acts as a reservoir of permanent hydration of the intervertebral disc, producing increased pressure, and improved fluid exchange and pH balance, leading to disc preservation.[38] Results of previous non-controlled studies suggest that GelStix[tm] implantation leads to a significant pain and disability relief four weeks after implantation in patients with discogenic pain.[39,40]

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Objectives

The purpose of this study is to evaluate the efficacy and safety of GelStix™ compared with sham control in patients with chronic discogenic low back pain that had no benefit from conservative care. The primary outcome will be the change in pain intensity between preoperative baseline and at six months post-intervention. Secondary outcomes include disability, quality of life outcome measures, the patient's global impression of change (PGIC) scale, the use of pain medication, and the disc degeneration process assessed by means of MRI.

We hypothesize that treatment with GelStix™ will lead to greater reduction in pain intensity at six months post-treatment compared to patients receiving sham treatment.

Trial design

This is a parallel group, randomized sham-controlled double-blind, multicentre trial to assess whether the GelStix^{tm} device is superior to sham in reducing pain intensity in patients with chronic discogenic low back pain. Patients are randomly allocated in a 1:1 ratio. Figure 2 provides a flow diagram of the progress through the enrolment, intervention allocation, follow-up, and data analysis phases of the trial.

Insert here Figure 2

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METHODS AND ANALYSIS

This protocol has been written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist. The study will be conducted in two regional hospitals: the Pain Management Center, Neurocenter of Southern Switzerland, Lugano, Switzerland, and the Department of Anaesthesiology and Pain Management Arnhem, Rijnstate Hospital, Arnhem, the Netherlands.

Participants

The target population is represented by patients suffering from discogenic low back pain with a baseline numeric rating scale (NRS) pain score ≥ 5/10 following at least twelve weeks conservative care.

Inclusion criteria:

- 18-66 years of age
- Lumbar DDD on MRI scan with Pfirrmann grade[41] 2, 3 or 4
- Discogenic pain confirmed by positive discography* of one or maximum two lumbar disc levels, and one negative control level
- Persistent predominant, nociceptive low back pain with a NRS score of ≥ 5/10, that worsens with axial loading and improves with recumbence of at least 12 weeks duration
- Failure to have symptoms resolved or reduced following at least 12 weeks conservative care (drug therapy and/or physiotherapy)
- Negative medial branches block results
- Legally competent and able to understand the nature, scope and aim of the clinical investigation

Exclusion criteria:

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- Radiculopathy caused by nerve root compression
- Frank herniations, extruded or sequestered fragments, bulge/protrusions in contact with any nerve root at the symptomatic level or >5mm in antero-posterior dimension
- Greater than grade 4 annular tear (Adams scale)[42]
- Disc height less than 3mm at the symptomatic level
- Severe symptomatic central, foraminal or lateral recess stenosis, spondylolysis, spondylolisthesis greater than I out of IV, acute fractures, or ankylosing spondylitis at any lumbar disc level
- Coagulopathy or oral anticoagulant therapy (except low-dose acetylsalicylic acid) in conditions that do not allow for a temporary discontinuation
- Active infection, systemically or localized
- Any disease process or condition that may make the effect of the treatment difficult to evaluate (e.g. cancer, substance abuse, etc.)
- Previous surgery at any lumbar disc level
- Body Mass Index (BMI) of ≥ 35 kg/m^2
- Females of childbearing age that are known to be pregnant or wishing to be pregnant during the study
- Psychological disorders or factors that may impact upon treatment outcomes or compliance (e.g. severe depressions)
- Participation in any other interventional study at the same time

*Procedure of provocative discography

Provocative discography will be performed by an experienced pain physician under strict sterile conditions. Thirty minutes before the intervention, intravenous antibiotics for prophylaxis will be administered. The patient will be positioned in the prone position on an X-ray permeable table. After subcutaneous anaesthetic injection of 2 ml mg of lidocaine 1%, the nucleus will be accessed with the

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two-needle technique with a 25-27 Gauge needle through the transforaminal, posterolateral approach, according to the technique described by Kallewaard et al.[3] Fluoroscopy will be used to identify spinal levels, guide the needle, and to confirm final needle position. The following variables will be monitored during the injection of the contrast solution: the opening pressure (the pressure at which contrast is first visible in the disc), the provocation pressure (the pressure greater than the opening pressure at which complaints of pain arise), and the peak pressure or the final pressure at the end of the procedure. Additionally, the total volume of the injected contrast solution, the Adams scale,[42] and the pain score measured by NRS per disc level will be recorded.

The procedure, per level, is continued until:[3]

- Concordant pain is reproduced at a level of ≥ 7/10 and/or
- The volume infused reaches 3.0 mL and/or
- The pressure rises to 50 psi above opening pressure

According to the guidelines of the IASP,[43] the symptomatic level and the one adjacent level are examined. A disc is only considered to be positive if concordant pain can be induced at the target level (symptomatic level); with an intensity of this pain of at least NRS 7, reproduced by a pressure of less than 50 psi above opening pressure; and if the control level is negative for provocation of pain. A control disc is considered a critical element for defining a positive discography, as it serves as an internal patient control disc and as a possible indicator of central sensitization.

Interventions

The GelStix™ implantation

For each participant, up to two levels will be treated. The CE marked GelStix™ Nucleus Augmentation Device system (STX-1835S, Replication Medical, Inc. – Cranbury, NJ, USA), will be implanted by an experienced pain physician familiar with the transforaminal posterolateral discography approach described above. The GelStix™ insertion will be performed under local anaesthesia with a single

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needle technique through the procedure-specific 18 Gauge needle (18GTXX165mm, Replication Medical, Inc. – Cranbury, NJ, USA). Up to three GelStixs will be implanted at each symptomatic disc level. Once the needle tip is located in the centre of the nucleus, the stylet will be removed from the needle. Then, the protective cap is removed from the preloaded GelStix^{tm} holder and the GelStix^{tm} holder is threaded onto the proximal end of the introducer needle. The holder stylet is pushed, driving the GelStix^{tm} completely into the introducer needle. The implant holder will then be removed and the needle stylet ('blunt push rod needle') is driven through the needle and bottomed out to deliver the GelStix^{tm} completely into the nucleus, keeping the needle tip centred in the nucleus (fig. 3-9). The procedure will be repeated to insert additional GelStix™. When resistance rises adding a second or third GelStix™, further insertion is discontinued. At the end of the procedure, the needle will be withdrawn, and a sterile bandage will be applied to the insertion site.

Insert here Figures 3-9.

The sham intervention

For the sham intervention the symptomatic discs will be injected with 1 ml of saline (NaCl 0.9%). Intradiscal saline injection (1 mL NaCl 0.9%) is safe[44] and has been used as a control/sham intervention in other randomized controlled [26,45,46]

Concomitant treatment

Starting two weeks after the intervention, participants of both study groups will be prescribed physiotherapy according to a study specific protocol. Session frequency will be once a week, for nine weeks. An experienced musculoskeletal physiotherapist will assess the patient before starting the post-intervention protocol, in order to determine the starting level for the exercises. Motor control and stabilization exercises will be instructed to the patients and they will get a leaflet with pictures of the exercises to perform at home/at work. Individual exercises include training of the deep

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abdominal muscles with the lumbar multifidus and the transversus abdominis. Moreover, to restore the function of the core muscles, all directions and their muscular chains will be trained. All patients will be instructed as to how to do exercises at home and will be asked to continue these exercises three times a week for six months. Continuation or modification of pain medication is permitted during the study period of twelve months.

Outcome measures

The primary outcome is the change in pain intensity, assessed by means of a pain diary, between preoperative baseline and at six months post-intervention in the GelStix^{tm}-treated compared to the sham-treated group. Pain intensity will be assessed employing an 11-point (i.e. 0–10) NRS with 0 meaning 'no pain' and '10' meaning 'worst possible pain'.[47] Three times daily pain scores will be assessed for five consecutive days around the intended measurement time. The mean NRS scores on the pain diary will furthermore be measured at one week, and one, three, and twelve months.

The secondary outcomes include:

- Disability, using the Oswestry Disability Index (ODI). The ODI is completed at baseline, and at three, six and twelve months. The ODI is a self-administered questionnaire, assessing the patient's level of pain and function during basic activities of daily living such as walking, personal care, standing, sleeping, etc.[48]
- Quality of life (QoL), quantified with the European Quality of Life Five Dimension Five Level Scale (EQ-5D-5L). The EQ-5D-5L will be completed at baseline and at three, six and twelve months. This questionnaire assesses health related quality of life in terms of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.[49] Additionally, the EuroQol Visual Analogue Scale (EQ VAS) records the respondent's self-rated health on a 20 cm vertical, visual analogue scale with endpoints labelled 'the best health you can imagine' and 'the worst health you can imagine'.

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- The Patient's Global Impression of Change (PGIC) scale will be measured at three, six and twelve months. This scale assesses the patient's own evaluation of improvement or deterioration over time on a 7-point Likert Scale rated from 'very much improved' to 'very much worse'.
- The use of pain medication will be assessed as the intake of analgesics at baseline, at one week, and at one, three, six and twelve months.
- The disc degeneration process will be assessed by means of MRI twelve months after treatment compared to baseline. Pfirrmann grade,[41] disc height, and the presence of high intensity zones (HIZ),[50] Modic signs,[51] and Schmorl's nodes[52] will be recorded.

Additionally, to assess the association between pain catastrophizing, surgical fear, state of depression and long-term outcome the following additional patient-reported outcome measures (PROMs) will be registered at baseline. Pain catastrophizing, defined as an exaggerated negative interpretation of the meaning of pain, will be measured by the Pain Catastrophizing Scale (PCS). Higher pain catastrophizing before intervention are related to lower perceived recovery.[53,54] Surgical fear will be measured by the Surgical Fear Questionnaire (SFQ) as a predictor of physical and emotional recovery.[53] State of depression will be assessed by the Hospital Anxiety and Depression Scale (HADS), a self-administered questionnaire developed to detect states of anxiety and depression in hospital out-patient clinics.[55] Moreover, pain self-efficacy will be assessed employing the Pain Self-Efficacy Questionnaire-I (PSEQ-I). This patient self-reported measurement instrument evaluates pain self-efficacy beliefs,[56] i.e. the degree of confidence a patient has in performing regular daily activities despite of pain. The presence of low levels of pain self-efficacy has been shown to be associated with high levels of disability in patients experiencing pain.[57,58]

The following additional data will be collected at baseline: sex, age, weight, height, smoking habits, previous treatment of discogenic pain, and neurological examination. Employment status baseline and

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at six and twelve months will be recorded. The proportion of patients unable to return to work will be an additional measure of efficacy of the treatment.

The success of blinding will be assessed at the end of the trial. Before unblinding, the patients and the blind observers will be asked to guess the patients' treatment and the answers will be compared with the actual treatments administered. Successful blinding procedures can reduce bias in clinical trials.[59,60]

The safety outcome of this study is the incidence and severity of complications and adverse events (AE's) including procedure-related complications at any time point in the study. The main expected adverse device effects are infection (local or discitis), bleeding, nerve damage and/or limited motion as a result of the procedure.

Sample size

Thirty patients per group will be required to have 80% power to detect a minimally clinically relevant difference of 1.5 points on the NRS between groups, with an estimated standard deviation (SD) of 2, and testing with an alpha of 5% (two-tailed). With an expected drop-out rate of 20%, 75 patients will be randomized**.**

Randomization

The Project Manager of the Clinical Trial Unit of the Ente Ospedaliero Cantonale (CTU-EOC), Bellinzona, Switzerland, will be in charge for computer generated block randomization lists stratified by centre (blocks of 4). The Project Manager will act as an independent person, not involved in any other aspect of the trial except administrative/financial issues. The study is patient- and observer-blinded, while the physician performing the study intervention will necessarily be aware of the

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treatment allocation. A web-based access to patient allocation codes will be provided to the physician in charge for GelStix[tm]/placebo injection. The treating team will be instructed not to communicate allocation to GelStix[tm] or placebo in any way, both to the patient and to other trial personnel. The "assessors", i.e., the investigators in charge for efficacy and safety assessments and the research nurses that may be in charge for questionnaires collection, and the personnel in charge of monitoring/data review and analysis will have no access to the randomization lists and will receive no information about patient treatment for the entire duration of the study. For patients still experiencing substantial discogenic pain at six months, the code can be broken at their request (after the assessment of the success of blinding). The patients initially allocated to the control group are then given the opportunity to cross-over to the GelStix[tm] treatment. Any other code breaks should occur only in circumstances when knowledge of the actual treatment is absolutely essential for further management of the patient e.g., in case of important AE's to ensure the most appropriate patient management.

Data collection and management

Study data will be collected on a case report form by the research team and will be entered in a research electronic data capture (REDCap) database.[61] The data will be associated to an unique trial identification number per patient. The database will be double-checked for missing data and data entry errors. The data from the REDCap database will be imported automatically in the latest version of R, a language for statistical computing. All study data will be archived for at least of 15 years after study termination.

Patient involvement

Patient with discogenic pain were involved at several stages of the trial, including the design and conduct of the trial. We carefully assessed the burden of the trial interventions on these patients. We

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will disseminate the main results to trial participants and will seek patient and public involvement in the development of an appropriate method of dissemination.

Statistical methods

Baseline characteristics will be described stratified by treatment allocation as mean and standard deviation or median and first and third quartile, and as count and percentage, as appropriate. In case of over 5% of missing data, we will use multiple imputation with fully conditional specification to impute the dataset. The number of imputations will be set to the percentage of incomplete patients. All subsequent analyses will be performed according to the intention to treat principle. A "per protocol" analysis will also be performed, excluding patients who are not evaluable for the primary endpoint because of dropout (e.g., consent withdrawal before completion of the six months observation period). Frequency and type of AE's and complications during the study will be described in the final report. Dropouts will be replaced up to the number of evaluable patients defined in the sample size calculation.

The primary outcome is change in pain (NRS) at six months compared to baseline. Mean values will be compared between groups using linear regression analysis, adjusted for treatment centre. In case of imbalance of baseline characteristics as judged by the trial steering committee, regression analyses will be further adjusted for potential confounders. Change from baseline in pain at other follow-up moments and change from baseline in continuous secondary outcome measures (i.e., disability (ODI) and health related quality of life [EQ-5D-5L], and disc height) will be analysed in a similar manner. PGIC scores will be dichotomized by taking "very much improved" and "much improved" to indicate treatment success. Pfirrmann grade will be dichotomized into grade 1 or 2 versus more than 2. Success rates on the PGIC, dichotomized Pfirrmann grade, and the presence of HIZ, Modic changes, and Schmorl's nodes will be compared between groups using logistic regression analysis adjusted for center.

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Univariable and multivariable logistic regression will be used to quantify crude and adjusted associations between PCS, SFQ, HADS, and PSEQ-I and treatment success. These analyses will be considered exploratory. The success of blinding will be assessed using the Sign test, testing whether the percentage of correct guesses differs from that expected by chance (i.e. 50%).

Monitoring

The research project will be monitored by a certified clinical monitor, which will review the data quality and will ensure that study activities are carried out in accordance with the protocol, good clinical practice and applicable regulatory requirements. This being a novel treatment method, a blinded interim analysis for futility will be planned for the primary outcome measure at T3 months after 40 patients (i.e. 20 in each arm of the study) have been enrolled. The study will be terminated in case the experimental arm performs significantly worse (as based on independent samples t-test or Mann-Whitney-U test) *and* the difference between groups is clinically relevant (i.e. 2 points or more on the NRS).

Limitations of the study

The limitations are those inherent to a prospective, randomized, sham-controlled study, including difficulty in recruiting patients due to potential patient refusal and strict exclusion criteria (e.g., protrusions in contact with any nerve root on the symptomatic level or >5mm), an insufficient number of patients, and adherence to a strict protocol that does not necessarily reflect real world daily practice. Recently performed strategies for achieving adequate participant enrolment to reach target sample size are the drafting and dispersal of an informative letter to referral colleagues in Switzerland and in the Netherlands, the introduction of a back pain treatment algorithm in the Pain Management Center in Lugano, indicating a clear algorithm to follow after negative medial branch block tests, indicating also the possibility for inclusion in the GelStix^{tm} study.

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Another limitation of this trial is the question whether intradiscal saline injection is a true placebo. For example, a recently published systematic review and meta-analysis of Manchikanti et al. showed that epidurally administered saline and saline with steroids may be both effective in managing low back and lower extremity pain.[62] On the other hand, saline has been routinely used as a sham intervention in several other intradiscal treatment studies such as the randomized controlled trial (RCT) of Kallewaard et al.,[26] which compared intradiscal methylene blue plus lidocaine to intradiscal saline plus lidocaine injection, and two the RCT's of Cao et al.[45] and Khot et al.[46] comparing intradiscal corticosteroid to saline injection in the treatment of discogenic low back pain.

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ETHICS AND DISSEMINATION

Research ethics approval and consent to participate

This trial has been approved by the Research Ethics Committee of the Canton Ticino, Switzerland (CE 2982) and by the Medical Ethical Committee Arnhem-Nijmegen, the Netherlands (2016-2944). All patients that agree to participate will sign an informed consent form provided by the independent observer. Any amendment to the protocol must as well be approved by this institution.

Confidentiality

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Subject confidentiality will be further ensured by utilizing subject identification code numbers. Direct access to source documents will be permitted for purposes of data review by authorized personnel involved in the trial and inspections. Patients' identity will not be disclosed to the person in charge for the statistical analysis and will not appear in any publication or public presentation of the study results. Results will be disseminated through international publications in peer reviewed journals, in addition to international conference presentations.

Funding statement

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Declaration of interest

The manufacturing Company Replication Medical, Inc. will cover the costs of the GelStix^{tm} material.

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This will be an unrestricted support and the manufacturer will not be involved in study design, data collection, analysis, interpretation and reporting/publication.

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Prof. Roberto S.G.M. Perez had an important role in the initiation of this study and helped substantially with the conception and design of the study. To our greatest regret, he passed away on 07.09.2017.

Author statement

EK, PM, JWK, LS, AC and SK designed the study. EK, PM, JWK, JD, LS, AC, PS, DK will conduct the study including patient recruitment and data collection. SK will conduct the data analysis and will conduct the interpretation of the data. JWK and PM drafted the manuscript with important intellectual input from EK, SK, AC, JD, MH, LS, PS, and DK. All authors approved the final manuscript. JWK, PM, JD, and EK will have complete access to the study data.

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Figure legends

Figure 1

1835S GelStix™. From left to right: 18 Gauge Needle, GelStix: dry, after 15 minutes hydration, after 30 minutes hydration, after 45 minutes hydration

Figure 2

Study flow chart

Figure 3

3A) Using fluoroscopic guidance, the needle is introduce using a standard posterolateral discography approach. 3B) The protective cap is removed from the preloaded implant holder. 3C) The implant holder is threaded onto the proximal end of the introducer needle. 3D) The holder stylet is pushed so that the implant is driven completely into the introducer needle. 3E) The implant holder is removed. The needle stylet is driven through the needle and bottomed out to deliver the GelStix^{tm} completely into the nucleus, keeping the needle tip centered in the nucleus. 3F) The needle tip will keep centered approximately in the nucleus and the procedure will be repeated to insert additional GelStix™.

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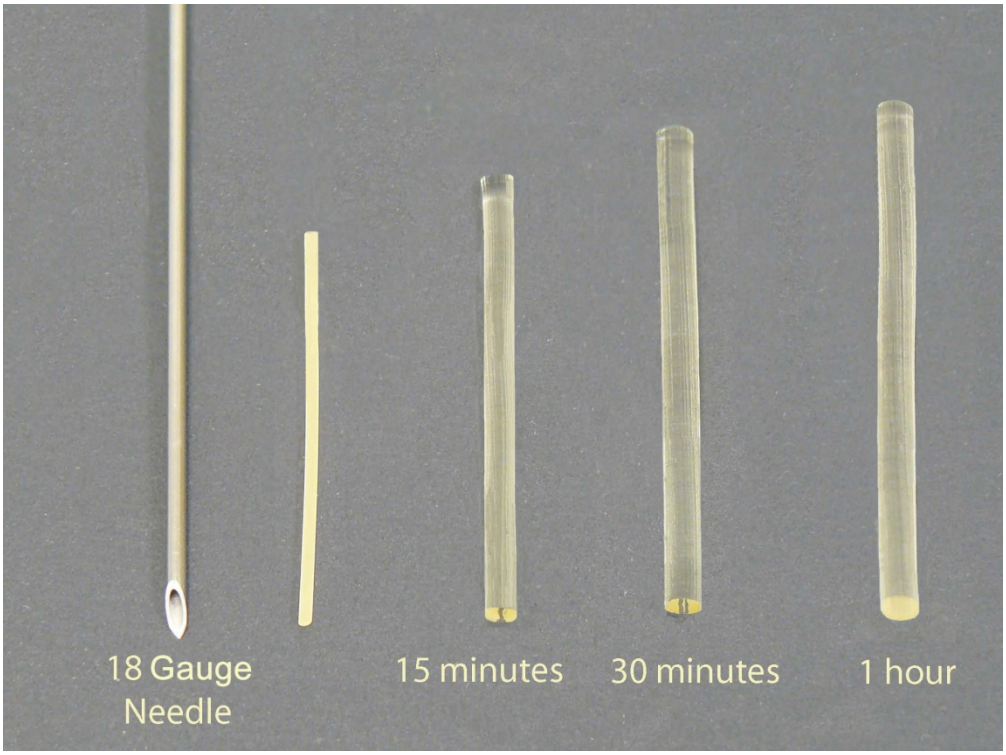
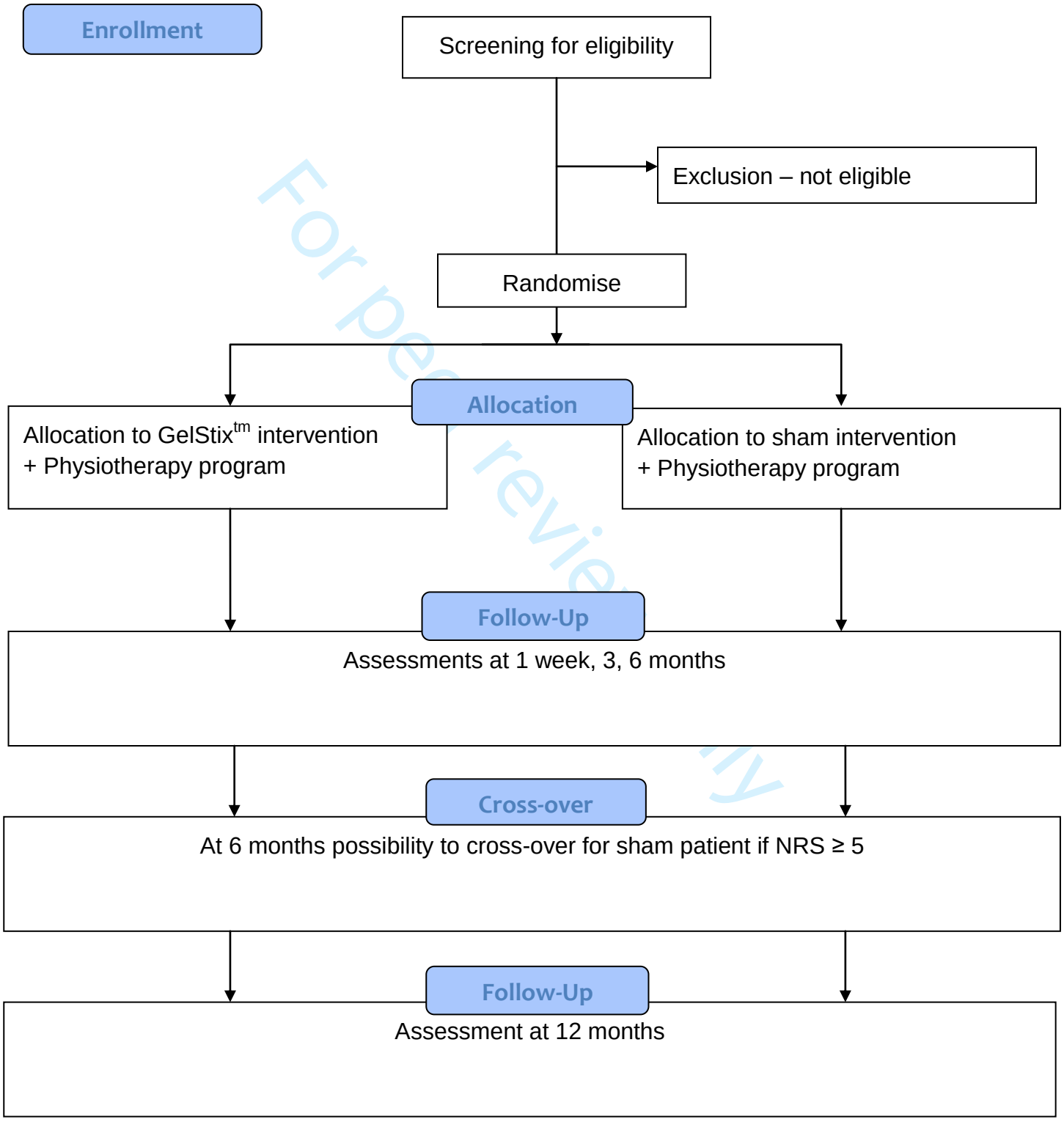


Figure 1
1835S GelStix™. From left to right: 18 Gauge Needle, GelStix: dry, after 15 minutes hydration, after 30 minutes hydration, after 45 minutes hydration

694x517mm (72 x 72 DPI)



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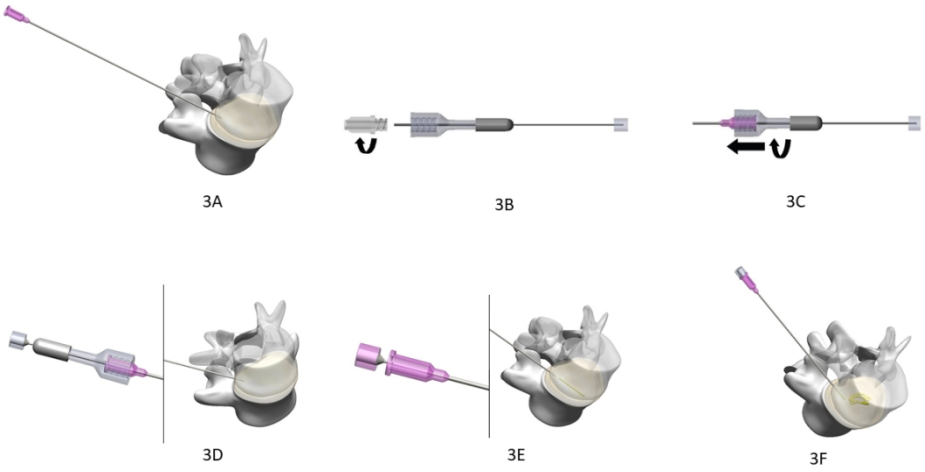

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338x190mm (96 x 96 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	#3	Date and version identifier	3
Funding	#4	Sources and types of financial, material, and other support	19
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 27
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	2
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	2
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and	NA

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		other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-7
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5-7
Objectives	#7	Specific objectives or hypotheses	7
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8

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Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8-10
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-11
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	16
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	NA
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12-14

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Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	12, Fig. 2
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	14
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	8, 17
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	14
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque,	14-15

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		sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	14-15
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	14-15
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	15
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	15

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Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	15
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16-17
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16-17
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and	17

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		competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	17
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	19
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	19

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Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	19
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	19
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	19
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	27
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15-16

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Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	NA
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	appendix 1
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

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BMJ Open

Efficacy of the Gelstix nucleus augmentation device for the treatment of chronic discogenic low back pain: protocol for a randomised, sham-controlled, double-blind, multicentre trial

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Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Radiology and imaging, Rheumatology
Keywords:	Back pain < ORTHOPAEDIC & TRAUMA SURGERY, PAIN MANAGEMENT, Musculoskeletal disorders < ORTHOPAEDIC & TRAUMA SURGERY

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Manuscripts

Efficacy of the Gelstix nucleus augmentation device for the treatment of chronic discogenic low back pain: protocol for a randomised, sham-controlled, double-blind, multicentre trial

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ABSTRACT

Introduction

Discogenic pain is the cause of pain in 26-40% of patients with for low back pain. Consensus about treatment of chronic discogenic low back pain is lacking and most treatment alternatives are supported by limited evidence. The percutaneous implantation of hydrogels into the nucleus pulposus represents a promising regenerative intradiscal therapy. The hydrogel 'GelStix™' is composed primarily of hydrolyzed polyacrylonitrile and acts as a reservoir of hydration, producing increased pressure and improved pH balance, potentially leading to disc preservation. We hypothesize that treatment with GelStix™ will lead to greater reduction in pain intensity at six months post-treatment compared to patients receiving sham treatment.

Methods and analysis

This is a parallel group, randomized sham-controlled double-blind, multicentre trial to assess whether the GelStix^{tm} device is superior to sham in reducing pain intensity in patients with chronic discogenic low back pain. The study will be conducted in two regional hospitals in Europe. Seventy-two participants will be randomized in a 1:1 ratio**.** The primary outcome will be the change in pain intensity between preoperative baseline and at six months post-intervention. Secondary outcomes were disability, quality of life, the patient's global impression of change scale, the use of pain medication, and the disc degeneration process assessed by means of MRI. For change in pain intensity, disability, health related quality of life, and disc height, mean values will be compared between groups using linear regression analysis, adjusted for treatment centre.

Ethics and dissemination

Ethics approval was obtained from the Ethics Committee of the Canton Ticino, Switzerland (CE2982) and by the Medical Ethical Committee Arnhem-Nijmegen, the Netherlands (2016-2944). All patients that agree to participate will be asked to sign an informed consent form. Results will be disseminated through international publications in peer reviewed journals, in addition to international conference presentations.

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Trial registration number NCT02763956

Protocol version 7.1, 18/11/2020

Keywords Back pain, pain management, musculoskeletal disorders

ARTICLE SUMMARY

Strengths and limitations of this study

- ►This will be the first prospective, randomized, controlled, multicentre trial assessing effectivity and safety of the GelStix™ Nucleus Augmentation Device compared to a sham control in patients with lumbar discogenic pain that had no benefit from conservative care.
- ►Means to reduce risk of bias are implemented, which includes an a-priori sample size calculation, an explicitly stated primary hypothesis to be tested, methodological rigor, double-blinding, randomization, adequate concealment of group allocation and the assessment of the success of blinding in participants and observers.
- ►This is also the first study that assesses the disc degeneration process and disc height by means of Magnetic Resonance Imaging (MRI) one year after GelStix™ implantation versus sham.
- ►All participants will also be treated according to a protocolized physiotherapy.
- ►The limitations are those inherent to a prospective, randomized sham-controlled double-blind study, including strict exclusion criteria and thus limited generalizability (e.g., protrusions in contact with any nerve root at the symptomatic level or >5mm, an insufficient number of patients, and adherence to a strict protocol that does not necessarily reflect real word daily practice).

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INTRODUCTION

Background and rationale

Discogenic low back pain is characterized by persistent, predominantly centralized axial low back pain that worsens with axial loading. It is associated with intervertebral disc degeneration without herniation,[1–4] and is thought to be the cause of pain in 26-40% of patients consulting a physician for low back pain.[5–9] The water-binding capabilities of the intervertebral disc diminish with aging[10] leading to progressive shrinking of the nucleus pulposus and loss of elasticity.[10–13] The cartilaginous endplate vascular flow decreases due to a progressive loss in vascularization leading to accumulation of cellular waste products, and an increasingly acidic environment.[10,14] A low pH around the discus is associated with discogenic pain.[15,16]

Medical history, physical examination, and imaging (e.g. magnetic resonance imaging (MRI)) provide inadequate sensitivity and specificity to accurately diagnose discogenic pain.[17–21] Despite an ongoing debate, moderate evidence supports diagnostic accuracy of provocative discography.[19,22–24] While previous studies suggest that high-pressure provocative discography may accelerate disc degeneration,[25–27] a recently published study suggests that low-pressure provocative discography, performed according to International Association for the Study of Pain (IASP) criteria, does not accelerate disc degeneration.[28]

Consensus about treatment of chronic discogenic low back pain is lacking and the majority of treatment alternatives is supported by limited evidence.[1,4] Conservative management includes anti-inflammatory drugs, physiotherapy, and multidisciplinary biopsychosocial rehabilitation.[29] If conservative treatment fails, (minimally) invasive treatments are considered.[1] Most minimally invasive treatments, such as intradiscal injections (e.g. with methylene blue) and thermal intradiscal/annular techniques (intradiscal electrothermal therapy (IDET), have been abandoned because of poor evidence.[30–32] A recent systematic review concluded that most minimal invasive treatments for discogenic low back have very low evidence; only biacuplasty has moderate evidence for a subgroup of patients with discogenic low back pain.[33]

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Fusion surgery and total disc replacement, although contemplated as possible therapies in some cases, are invasive interventions associated with risk of adjacent segment disorder and morbidity.[4,34] In addition, fusion surgery is not superior to conservative treatment with multidisciplinary biopsychosocial rehabilitation and physiotherapy.[35,36] Recently, with the emergence of new frequencies (burst, dorsal root ganglion stimulation, high frequency-10Hz), low back pain has become a good treatment option for neuromodulation. Considering the fact that neuromodulation is a more invasive treatment the need is great to find evidence for minimal invasive treatment for chronic discogenic low back pain.[37,38]

Therefore, treatment options filling the gap between conservative care and invasive surgical intervention are urgently needed. Currently the first studies are published showing effect of the use of platelet-rich plasma (PRP) and mesenchymal signaling cells (MSCs) for discogenic pain. Notably, no intervention has multiple RCT's published yet.[39] The implantation of hydrogels into the nucleus pulposus represents a promising regenerative intradiscal therapy, in particular in patients with early or moderate disc degeneration not responding to conservative care.[40,41] The hydrogel containing 'GelStix™ Nucleus Augmentation Device' (hereafter called GelStix™) is composed primarily of hydrolyzed polyacrylonitrile (HPAN). The GelStix™ is shaped in the form of an elongated matchstick and can be inserted percutaneously into the nucleus through a needle. Once implanted, the GelStix™ absorbs the body's own fluids and expands around tenfold in volume (see Fig. 1).

Insert here Figure 1

The GelStix™ material acts as a reservoir of permanent hydration of the intervertebral disc, producing increased pressure, and improved fluid exchange and pH balance, leading to disc preservation.[42] Results of previous non-controlled studies suggest that GelStix[tm] implantation leads to a significant pain and disability relief four weeks after implantation in patients with discogenic pain.[43,44]

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Objectives

The purpose of this study is to evaluate the efficacy and safety of GelStix™ compared with sham control in patients with chronic discogenic low back pain that had no benefit from conservative care. The primary outcome will be the change in pain intensity between preoperative baseline and at six months post-intervention. Secondary outcomes include disability, quality of life outcome measures, the patient's global impression of change (PGIC) scale, the use of pain medication, and the disc degeneration process assessed by means of MRI.

We hypothesize that treatment with GelStix™ will lead to greater reduction in pain intensity at six months post-treatment compared to patients receiving sham treatment.

Trial design

This is a parallel group, randomized sham-controlled double-blind, multicentre trial to assess whether the GelStix^{tm} device is superior to sham in reducing pain intensity in patients with chronic discogenic low back pain. Patients are randomly allocated in a 1:1 ratio. Figure 2 provides a flow diagram of the progress through the enrolment, intervention allocation, follow-up, and data analysis phases of the trial.

Insert here Figure 2

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METHODS AND ANALYSIS

This protocol has been written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist. The study will be conducted in two regional hospitals in Europe: the Pain Management Center, Neurocenter of Southern Switzerland, Lugano, Switzerland, and the Department of Anaesthesiology and Pain Management Arnhem, Rijnstate Hospital, Arnhem, the Netherlands. Recruitment started in April 2016 and we included 42 participants till now. We expect to complete the study in 2025.

Participants

The target population is represented by patients suffering from discogenic low back pain with a baseline numeric rating scale (NRS) pain score ≥ 5/10 following at least twelve weeks conservative care.

Inclusion criteria:

- 18-66 years of age
- Lumbar DDD on MRI scan with Pfirrmann grade[45] 2, 3 or 4
- Discogenic pain confirmed by positive discography* of one or maximum two lumbar disc levels, and one negative control level
- Persistent predominant, nociceptive low back pain with a NRS score of ≥ 5/10, that worsens with axial loading and improves with recumbence of at least 12 weeks duration
- Failure to have symptoms resolved or reduced following at least 12 weeks conservative care (drug therapy and/or physiotherapy)
- Negative medial branches block results
- Legally competent and able to understand the nature, scope and aim of the clinical investigation

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Exclusion criteria:

- Radiculopathy caused by nerve root compression
- Frank herniations, extruded or sequestered fragments, bulge/protrusions in contact with any nerve root at the symptomatic level or >5mm in antero-posterior dimension
- Greater than grade 4 annular tear (Adams scale)[46]
- Disc height less than 3mm at the symptomatic level
- Severe symptomatic central, foraminal or lateral recess stenosis, spondylolysis, spondylolisthesis greater than I out of IV, acute fractures, or ankylosing spondylitis at any lumbar disc level
- Coagulopathy or oral anticoagulant therapy (except low-dose acetylsalicylic acid) in conditions that do not allow for a temporary discontinuation
- Active infection, systemically or localized
- Any disease process or condition that may make the effect of the treatment difficult to evaluate (e.g. cancer, substance abuse, etc.)
- Previous surgery at any lumbar disc level
- Body Mass Index (BMI) of ≥ 35 kg/m^2
- Females of childbearing age that are known to be pregnant or wishing to be pregnant during the study
- Psychological disorders or factors that may impact upon treatment outcomes or compliance (e.g. severe depressions)
- Participation in any other interventional study at the same time

*Procedure of provocative discography

Provocative discography will be performed by an experienced pain physician under strict sterile conditions. Thirty minutes before the intervention, intravenous antibiotics for prophylaxis will be

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administered. The patient will be positioned in the prone position on an X-ray permeable table. After subcutaneous anaesthetic injection of 2 ml mg of lidocaine 1%, the nucleus will be accessed with the two-needle technique with a 25-27 Gauge needle through the transforaminal, posterolateral approach, according to the technique described by Kallewaard et al.[3] Fluoroscopy will be used to identify spinal levels, guide the needle, and to confirm final needle position. The following variables will be monitored during the injection of the contrast solution: the opening pressure (the pressure at which contrast is first visible in the disc), the provocation pressure (the pressure greater than the opening pressure at which complaints of pain arise), and the peak pressure or the final pressure at the end of the procedure. Additionally, the total volume of the injected contrast solution, the Adams scale,[46] and the pain score measured by NRS per disc level will be recorded.

The procedure, per level, is continued until:[3]

- Concordant pain is reproduced at a level of ≥ 7/10 and/or
- The volume infused reaches 3.0 mL and/or
- The pressure rises to 50 psi above opening pressure

According to the guidelines of the IASP,[47] the symptomatic level and the one adjacent level are examined. A disc is only considered to be positive if concordant pain can be induced at the target level (symptomatic level); with an intensity of this pain of at least NRS 7, reproduced by a pressure of less than 50 psi above opening pressure; and if the control level is negative for provocation of pain. A control disc is considered a critical element for defining a positive discography, as it serves as an internal patient control disc and as a possible indicator of central sensitization.

Interventions

The GelStix™ implantation

For each participant, up to two levels will be treated. The CE marked GelStix™ Nucleus Augmentation Device system (STX-1835S, Replication Medical, Inc. – Cranbury, NJ, USA), will be implanted by an

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experienced pain physician familiar with the transforaminal posterolateral discography approach described above. The GelStix™ insertion will be performed under local anaesthesia with a single needle technique through the procedure-specific 18 Gauge needle (18GTXX165mm, Replication Medical, Inc. – Cranbury, NJ, USA). Up to three GelStixs will be implanted at each symptomatic disc level. Once the needle tip is located in the centre of the nucleus, the stylet will be removed from the needle. Then, the protective cap is removed from the preloaded GelStix^{tm} holder and the GelStix^{tm} holder is threaded onto the proximal end of the introducer needle. The holder stylet is pushed, driving the GelStix^{tm} completely into the introducer needle. The implant holder will then be removed and the needle stylet ('blunt push rod needle') is driven through the needle and bottomed out to deliver the GelStix^{tm} completely into the nucleus, keeping the needle tip centred in the nucleus (fig. 3A-3F). The procedure will be repeated to insert additional GelStix™. When resistance rises adding a second or third GelStix™, further insertion is discontinued. At the end of the procedure, the needle will be withdrawn, and a sterile bandage will be applied to the insertion site.

Insert here Figure 3

<u>The sham intervention</u>

For the sham intervention the symptomatic discs will be injected with 1 ml of saline (NaCl 0.9%). Intradiscal saline injection (1 mL NaCl 0.9%) is safe[48] and has been used as a control/sham intervention in other randomized controlled [30,49,50]

<u>Concomitant treatment</u>

Starting two weeks after the intervention, participants of both study groups will be prescribed physiotherapy according to a study specific protocol. Session frequency will be once a week, for nine weeks. An experienced musculoskeletal physiotherapist will assess the patient before starting the post-intervention protocol, in order to determine the starting level for the exercises. Motor control

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and stabilization exercises will be instructed to the patients and they will get a leaflet with pictures of the exercises to perform at home/at work. Individual exercises include training of the deep abdominal muscles with the lumbar multifidus and the transversus abdominis. Moreover, to restore the function of the core muscles, all directions and their muscular chains will be trained. All patients will be instructed as to how to do exercises at home and will be asked to continue these exercises three times a week for six months. Continuation or modification of pain medication is permitted during the study period of twelve months.

Outcome measures

The primary outcome is the change in pain intensity, assessed by means of a pain diary, between preoperative baseline and at six months post-intervention in the GelStix^{tm}-treated compared to the sham-treated group. Pain intensity will be assessed employing an 11-point (i.e. 0–10) NRS with 0 meaning 'no pain' and '10' meaning 'worst possible pain'.[51] Three times daily pain scores will be assessed for five consecutive days around the intended measurement time. The mean NRS scores on the pain diary will furthermore be measured at one week, and one, three, and twelve months.

The secondary outcomes include:

- Disability, using the Oswestry Disability Index (ODI). The ODI is completed at baseline, and at three, six and twelve months. The ODI is a self-administered questionnaire, assessing the patient's level of pain and function during basic activities of daily living such as walking, personal care, standing, sleeping, etc.[52]
- Quality of life (QoL), quantified with the European Quality of Life Five Dimension Five Level Scale (EQ-5D-5L). The EQ-5D-5L will be completed at baseline and at three, six and twelve months. This questionnaire assesses health related quality of life in terms of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.[53] Additionally, the EuroQol Visual Analogue Scale (EQ VAS) records the respondent's self-rated health on a 20

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cm vertical, visual analogue scale with endpoints labelled 'the best health you can imagine' and 'the worst health you can imagine'.

- The Patient's Global Impression of Change (PGIC) scale will be measured at three, six and twelve months. This scale assesses the patient's own evaluation of improvement or deterioration over time on a 7-point Likert Scale rated from 'very much improved' to 'very much worse'.
- The use of pain medication will be assessed as the intake of analgesics at baseline, at one week, and at one, three, six and twelve months.
- The disc degeneration process will be assessed by means of MRI twelve months after treatment compared to baseline. Pfirrmann grade,[45] disc height, and the presence of high intensity zones (HIZ),[54] Modic signs,[55] and Schmorl's nodes[56] will be recorded.

Additionally, to assess the association between pain catastrophizing, surgical fear, state of depression and long-term outcome the following additional patient-reported outcome measures (PROMs) will be registered at baseline. Pain catastrophizing, defined as an exaggerated negative interpretation of the meaning of pain, will be measured by the Pain Catastrophizing Scale (PCS). Higher pain catastrophizing before intervention are related to lower perceived recovery.[57,58] Surgical fear will be measured by the Surgical Fear Questionnaire (SFQ) as a predictor of physical and emotional recovery.[57] State of depression will be assessed by the Hospital Anxiety and Depression Scale (HADS), a self-administered questionnaire developed to detect states of anxiety and depression in hospital out-patient clinics.[59] Moreover, pain self-efficacy will be assessed employing the Pain Self-Efficacy Questionnaire-I (PSEQ-I). This patient self-reported measurement instrument evaluates pain self-efficacy beliefs,[60] i.e. the degree of confidence a patient has in performing regular daily activities despite of pain. The presence of low levels of pain self-efficacy has been shown to be associated with high levels of disability in patients experiencing pain.[61,62]

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The following additional data will be collected at baseline: sex, age, weight, height, smoking habits, previous treatment of discogenic pain, and neurological examination. Employment status baseline and at six and twelve months will be recorded. The proportion of patients unable to return to work will be an additional measure of efficacy of the treatment.

The success of blinding will be assessed at the end of the trial. Before unblinding, the patients and the blind observers will be asked to guess the patients' treatment and the answers will be compared with the actual treatments administered. Successful blinding procedures can reduce bias in clinical trials.[63,64]

The safety outcome of this study is the incidence and severity of complications and adverse events (AE's) including procedure-related complications at any time point in the study. The main expected adverse device effects are infection (local or discitis), bleeding, nerve damage and/or limited motion as a result of the procedure.

Sample size

Twenty-eight patients per group will be required to have 80% power to detect a minimally clinically relevant difference of 1.5 points on the NRS between groups, with an estimated standard deviation (SD) of 2, based on the pooled SD of NRS scores of similar patients in the RCT of Kallewaard et al.,[30] and testing with an alpha of 5% (two-tailed). With an expected drop-out rate of about 20%, a total of 72 patients will be randomized**.**

Randomization

The Project Manager of the Clinical Trial Unit of the Ente Ospedaliero Cantonale (CTU-EOC), Bellinzona, Switzerland, will be in charge for computer generated block randomization lists stratified

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by centre (blocks of 4). The Project Manager will act as an independent person, not involved in any other aspect of the trial except administrative/financial issues. The study is patient- and observer-blinded, while the physician performing the study intervention will necessarily be aware of the treatment allocation. A web-based access to patient allocation codes will be provided to the physician in charge for GelStix^{tm}/placebo injection. The treating team will be instructed not to communicate allocation to GelStix^{tm} or placebo in any way, both to the patient and to other trial personnel. The "assessors", i.e., the investigators in charge for efficacy and safety assessments and the research nurses that may be in charge for questionnaires collection, and the personnel in charge of monitoring/data review and analysis will have no access to the randomization lists and will receive no information about patient treatment for the entire duration of the study. For patients still experiencing substantial discogenic pain at six months, the code can be broken at their request (after the assessment of the success of blinding). The patients initially allocated to the control group are then given the opportunity to cross-over to the GelStix^{tm} treatment. Any other code breaks should occur only in circumstances when knowledge of the actual treatment is absolutely essential for further management of the patient e.g., in case of important AE's to ensure the most appropriate patient management.

Data collection and management

Study data will be collected on a case report form by the research team and will be entered in a research electronic data capture (REDCap) database.[65] The data will be associated to a unique trial identification number per patient. The database will be double-checked for missing data and data entry errors. The data from the REDCap database will be imported automatically in the latest version of R, a language for statistical computing. All study data will be archived for at least of 15 years after study termination.

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Statistical methods

Baseline characteristics will be described stratified by treatment allocation as mean and standard deviation or median and first and third quartile, and as count and percentage, as appropriate. In case of over 5% of missing data, we will use multiple imputation with fully conditional specification to impute the dataset. The number of imputations will be set to the percentage of incomplete patients. All subsequent analyses will be performed according to the intention to treat principle. A "per protocol" analysis will also be performed, excluding patients who are not evaluable for the primary endpoint because of dropout (e.g., consent withdrawal before completion of the six months observation period). Frequency and type of AE's and complications during the study will be described in the final report. Dropouts will be replaced up to the number of evaluable patients defined in the sample size calculation.

The primary outcome is change in pain (NRS) at six months compared to baseline. Mean values will be compared between groups using linear regression analysis, adjusted for treatment centre. In case of imbalance of baseline characteristics as judged by the trial steering committee, regression analyses will be further adjusted for potential confounders. This adjustment will be performed as stratified randomization induces correlated observations, which should be accounted for. By adjusting for treatment center, the analyses yield correct p-values and confidence intervals with the correct coverage, and results in more power compared to unadjusted analyses.[66]

Change from baseline in pain at other follow-up moments and change from baseline in continuous secondary outcome measures (i.e., disability (ODI) and health related quality of life [EQ-5D-5L], and disc height) will be analysed in a similar manner. PGIC scores will be dichotomized by taking "very much improved" and "much improved" to indicate treatment success. Pfirrmann grade will be dichotomized into grade 1 or 2 versus more than 2. Success rates on the PGIC, dichotomized Pfirrmann grade, and the presence of HIZ, Modic changes, and Schmorl's nodes will be compared between groups using logistic regression analysis adjusted for center.

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Univariable and multivariable logistic regression will be used to quantify crude and adjusted associations between PCS, SFQ, HADS, and PSEQ-I and treatment success. These analyses will be considered exploratory. The success of blinding will be assessed using the Sign test, testing whether the percentage of correct guesses differs from that expected by chance (i.e. 50%).

Monitoring

The research project will be monitored by a certified clinical monitor, which will review the data quality and will ensure that study activities are carried out in accordance with the protocol, good clinical practice and applicable regulatory requirements. This being a novel treatment method, a blinded interim analysis for futility will be planned for the primary outcome measure at T3 months after 40 patients (i.e. 20 in each arm of the study) have been enrolled. The study will be terminated in case the experimental arm performs significantly worse (as based on independent samples t-test or Mann-Whitney-U test) *and* the difference between groups is clinically relevant (i.e. 2 points or more on the NRS).

Limitations of the study

The limitations are those inherent to a prospective, randomized, sham-controlled study, including difficulty in recruiting patients due to potential patient refusal and strict exclusion criteria (e.g., protrusions in contact with any nerve root on the symptomatic level or >5mm), an insufficient number of patients, and adherence to a strict protocol that does not necessarily reflect real world daily practice. Recently performed strategies for achieving adequate participant enrolment to reach target sample size are the drafting and dispersal of an informative letter to referral colleagues in Switzerland and in the Netherlands, the introduction of a back pain treatment algorithm in the Pain Management Center in Lugano, indicating a clear algorithm to follow after negative medial branch block tests, indicating also the possibility for inclusion in the GelStix^{tm} study.

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Another limitation of this trial is the question whether intradiscal saline injection is a true placebo, as it may have active effects. For example, a recently published systematic review and meta-analysis of Manchikanti et al. showed that epidurally administered saline and saline with steroids may be both effective in managing low back and lower extremity pain.[67] On the other hand, saline has been routinely used as a sham intervention in several other intradiscal treatment studies such as the randomized controlled trial (RCT) of Kallewaard et al.,[30] which compared intradiscal methylene blue plus lidocaine to intradiscal saline plus lidocaine injection, and two the RCT's of Cao et al.[49] and Khot et al.[50] comparing intradiscal corticosteroid to saline injection in the treatment of discogenic low back pain. To reduce the risk of a bias due to the uncertainty saline injection being a true placebo, a third 'no treatment group' (receiving only physiotherapy treatment) could be added to this study. However, we regard adding a third 'no treatment group' to this study not feasible, mainly because of the expected difficulties in patient recruitment.

Patient and public involvement

Patient with discogenic pain were involved at several stages of the trial, including the design and conduct of the trial. We carefully assessed the burden of the trial interventions on these patients. We will disseminate the main results to trial participants and will seek patient and public involvement in the development of an appropriate method of dissemination.

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ETHICS AND DISSEMINATION

Research ethics approval and consent to participate

This trial has been approved by the Research Ethics Committee of the Canton Ticino, Switzerland (CE 2982) and by the Medical Ethical Committee Arnhem-Nijmegen, the Netherlands (2016-2944). All patients that agree to participate will sign an informed consent form provided by the independent observer. Any amendment to the protocol must as well be approved by this institution.

Confidentiality

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Subject confidentiality will be further ensured by utilizing subject identification code numbers. Direct access to source documents will be permitted for purposes of data review by authorized personnel involved in the trial and inspections. Patients' identity will not be disclosed to the person in charge for the statistical analysis and will not appear in any publication or public presentation of the study results.

Dissemination

Results will be disseminated through international publications in peer reviewed journals, in addition to international conference presentations.

Funding statement

This research is not supported by a topic-specific grant from any funding agency in the public, commercial or not-for-profit sectors. Research personnel will in part be paid by previous grants that were not awarded for this specific study. The manufacturing company Replication Medical, Inc. will cover the costs of the GelStix^{tm} material. This will be an unrestricted support and the manufacturer

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will not be involved in study design, data collection, analysis, interpretation, and reporting/publication.

Competing interest

None declared

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Prof. Roberto S.G.M. Perez had an important role in the initiation of this study and helped substantially with the conception and design of the study. To our greatest regret, he passed away on 07.09.2017.

Author statement

EK, PM, JWK, LS, AC and SK designed the study. EK, PM, JWK, JD, LS, AC, PS, DK will conduct the study including patient recruitment and data collection. SK will conduct the data analysis and will conduct the interpretation of the data. EK drafted the manuscript with important intellectual input from JWK, PM, SK, AC, JD, MH, LS, PS, and DK. All authors approved the final manuscript. EK, JWK, PM, and JD will have complete access to the study data.

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Figure legends

Figure 1

1835S GelStix™. From left to right: 18 Gauge Needle, GelStix: dry, after 15 minutes hydration, after 30 minutes hydration, after 45 minutes hydration

Figure 2

Study flow chart

Figure 3

3A) Using fluoroscopic guidance, the needle is introduce using a standard posterolateral discography approach. 3B) The protective cap is removed from the preloaded implant holder. 3C) The implant holder is threaded onto the proximal end of the introducer needle. 3D) The holder stylet is pushed so that the implant is driven completely into the introducer needle. 3E) The implant holder is removed. The needle stylet is driven through the needle and bottomed out to deliver the GelStix^{tm} completely into the nucleus, keeping the needle tip centered in the nucleus. 3F) The needle tip will keep centered approximately in the nucleus and the procedure will be repeated to insert additional GelStix™.

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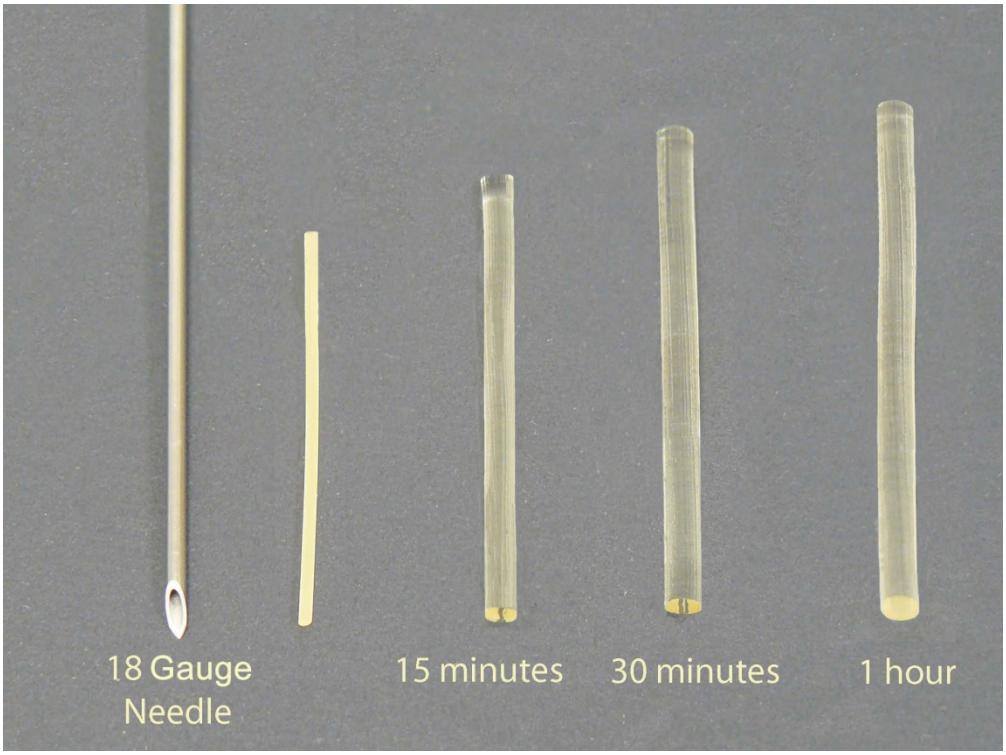
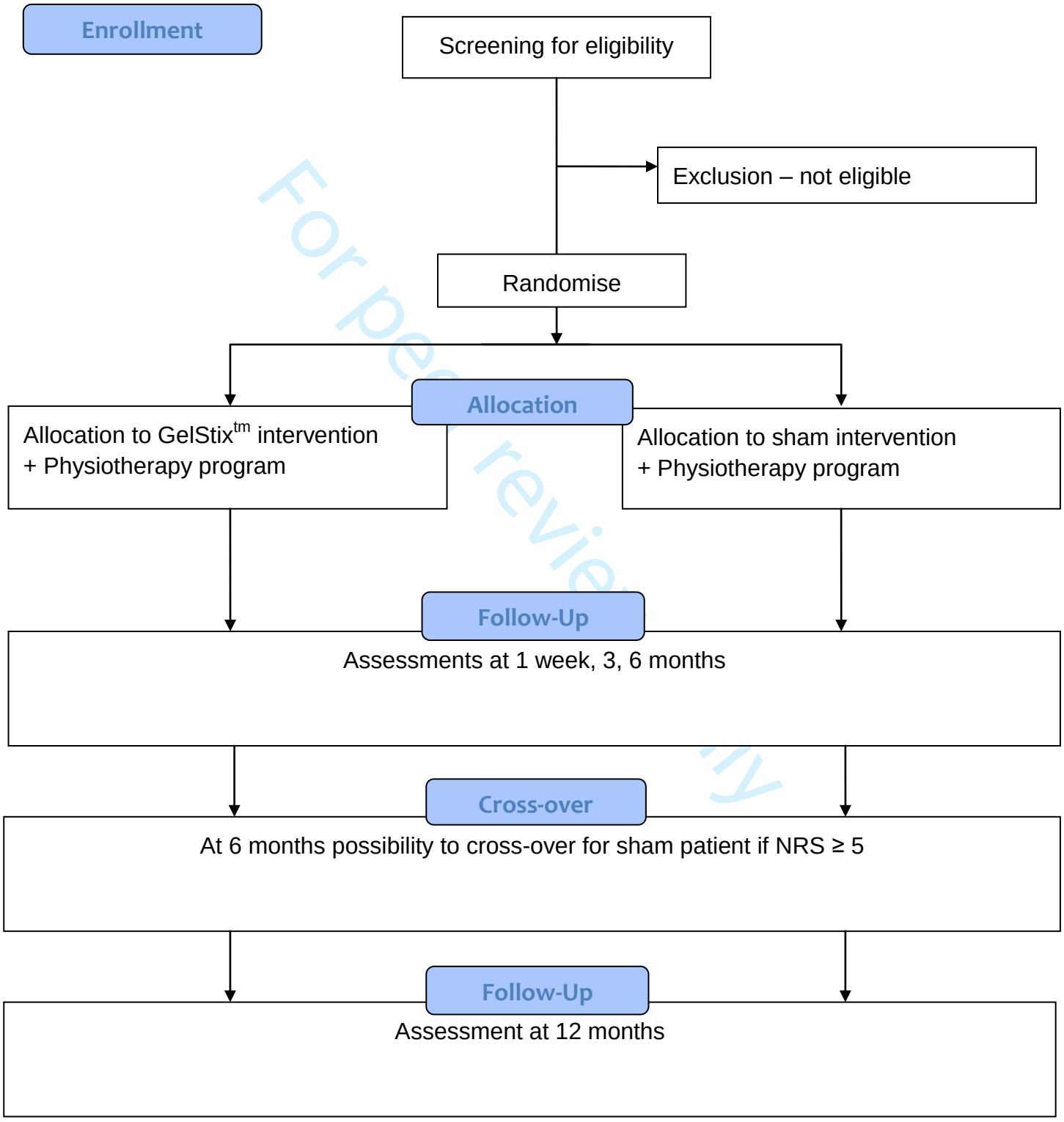


Figure 1
1835S GelStix™. From left to right: 18 Gauge Needle, GelStix: dry, after 15 minutes hydration, after 30 minutes hydration, after 45 minutes hydration

694x517mm (72 x 72 DPI)



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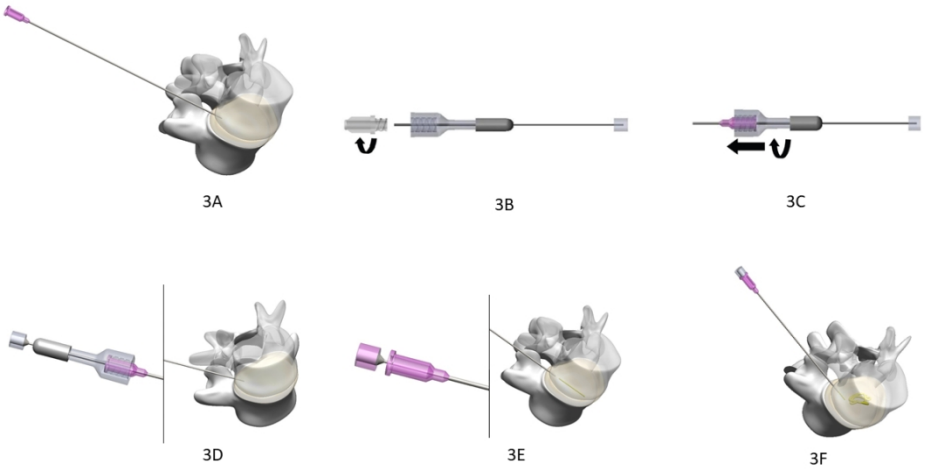

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338x190mm (96 x 96 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	#3	Date and version identifier	3
Funding	#4	Sources and types of financial, material, and other support	19
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 27
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	2
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	2
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and	NA

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		other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-7
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5-7
Objectives	#7	Specific objectives or hypotheses	7
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8

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Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8-10
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-11
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	16
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	NA
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12-14

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Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	12, Fig. 2
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	14
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	8, 17
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	14
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque,	14-15

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		sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	14-15
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	14-15
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	15
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	15

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Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	15
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16-17
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16-17
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and	17

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		competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	17
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	19
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	19

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Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	19
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	19
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	19
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	27
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15-16

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Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	NA
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	appendix 1
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

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